

EXHIBIT 9

Carcinogenicity of talc and acrylonitrile



In June, 2024, a Working Group of 29 scientists from 13 countries met at the International Agency for Research on Cancer (IARC) in Lyon, France, to finalise their evaluation of the carcinogenicity of talc and acrylonitrile.

Acrylonitrile was classified as “carcinogenic to humans” (Group 1) based on “sufficient” evidence for cancer in humans. There was also “sufficient” evidence for cancer in experimental animals and “strong” mechanistic evidence in experimental systems. Talc was classified as “probably carcinogenic to humans” (Group 2A) based on a combination of “limited” evidence for cancer in humans, “sufficient” evidence for cancer in experimental animals, and “strong” mechanistic evidence in human primary cells and experimental systems. This evaluation supersedes the previous classifications of “talc not containing asbestos or asbestiform fibres” and “perineal use of talc-based body powder” in Volume 93 of the *IARC Monographs*. These assessments will be published in Volume 136 of the *IARC Monographs*.¹ “Talc containing asbestos” was not re-evaluated and retains its classification within “asbestos” (Group 1) from Volume 100C.

Acrylonitrile, a high-production-volume chemical, is mostly used as a monomer to prepare polymers for the manufacture of fibres (textiles, clothing, and carpets) and resins, synthetic rubber, and plastics. In workers, exposure occurs mainly in production industries. For the general population, exposure mainly occurs via tobacco smoke. Acrylonitrile is readily absorbed after inhalation or ingestion, and through the skin, and is systemically distributed. Absorbed acrylonitrile is mainly metabolised and then excreted in the urine. Major metabolic pathways in humans and rats include activation to 2-cyanoethylene oxide predominantly by cytochrome P450E1 and conjugation with glutathione, eventually yielding

2-cyanoethylmercapturic acid, which is excreted in urine.

There was “sufficient” evidence that acrylonitrile causes lung cancer in humans and “limited” evidence for bladder cancer based on data from occupational studies. In a high-quality pooled cohort of eight facilities covering the major sectors of acrylonitrile production and use, a quantitative exposure–response association was observed for lung cancer mortality, after accounting for major sources of confounding² and healthy worker survivor bias. Associations between acrylonitrile exposure and lung cancer were also observed in other studies, including a large case-control study.³ For bladder cancer, there was a positive exposure–response relationship for mortality based on categories of participants’ individual average exposure in the pooled cohort study² and imprecise associations in the other cohorts; thus, chance, bias, and confounding could not be reasonably ruled out.

In B6C3F1 mice, acrylonitrile caused forestomach squamous cell carcinoma in males and females when administered by gavage.⁴ When administered orally,⁵ acrylonitrile caused brain astrocytoma and Zymbal gland carcinoma in male and female Sprague-Dawley (SD) rats; spinal cord astrocytoma, forestomach squamous cell carcinoma, and intestinal adenocarcinoma in males; and mammary gland carcinoma in females. In a two-generation inhalation study in SD rats, acrylonitrile caused oligodendroglioma and Zymbal gland carcinoma in the male offspring and oligodendroglioma, extrahepatic angiosarcoma, mammary gland adenocarcinoma, and lymphohaematopoietic tumours in the female offspring.⁶

Multiple studies in experimental systems reported that acrylonitrile binds to nucleic acids, haemoglobin, and multiple tissue proteins; however, in rats, N7-oxoethylguanine adduct was observed marginally; no DNA

adduct formation was reported in exposed humans. Acrylonitrile is genotoxic; it induces genetic alterations, including mutations, in experimental systems ranging from bacteria to rodents,^{7,8} typically requiring metabolic activation. Acrylonitrile induces oxidative stress, including increased reactive oxygen species generation, oxidative damage to DNA, and altered levels of antioxidant proteins in vivo and in vitro. Acrylonitrile causes immortalisation as shown by induction of anchorage-independent growth, p53 and p21^{WAF1} biomarkers of senescence, and cell transformation in vitro. Acrylonitrile alters cell proliferation, cell death, or nutrient supply; in rodents, acrylonitrile consistently induced hyperplasia in multiple tissues at several doses and exposures up to 2 years.⁴

The agent “talc” was defined as mineral or synthetic talc, a hydrated magnesium silicate, including lamellar and fibrous (which includes asbestiform fibres) forms of talc. Asbestiform talc is not asbestos; however, asbestos has been reported to be present in some talc ores and talc products as a contaminant. Industry standards used to assess talc-based cosmetic and pharmaceutical products have often been insufficiently sensitive to rule out asbestos contamination. Talc is a high-production-volume mineral used in plastics, ceramics, paint, paper, roofing materials, rubber products, animal feed, food, fertilisers, cosmetics, and pharmaceuticals. Talc is also used in clinical settings for pleurodesis. High occupational exposure to talc dust occurs during mining and milling, mainly via inhalation. Exposures can also occur among workers in downstream manufacturing industries. The general population is exposed via ingestion, inhalation, dermal, or perineal routes. In humans, talc inhaled or injected into the pleura during pleurodesis is retained in the lungs even after cessation of exposure. In human biopsies, talc was

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Declaration of interests

All Working Group Members declare no competing interests.

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None

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None

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Declaration of interests

BB is employed by RJ Lee Group, an analytical laboratory and scientific consulting firm, with business interests that may be affected by the outcome of this present meeting. He provides expert opinions on behalf of law firms in connection with expert testimony for defendants in talc litigation. BJ serves as an expert witness in talc litigation. CRK is an independent consulting toxicologist who has provided consulting services for more than 20 years to the Acrylonitrile Group, and only recently to Eurotalc. KM is a paid consultant to Eurotalc and the Acrylonitrile Group to observe the proceedings on their behalf.

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identified in multiple pelvic sites distant from the perineum, including the ovary. In rabbits and rats, intrapleural exposure to talc leads to translocation and deposition in lungs and other organs. In animal studies, inhaled talc is cleared from the lungs within 4–12 months after up to 4 weeks of exposure. Most animal studies report no translocation from the perineal region to the ovary. Orally ingested talc is excreted shortly after dosing, and no or negligible intestinal absorption or translocation to other organs has been observed.

There was “limited” evidence that talc causes ovarian cancer in humans. Most of the available studies assessed use of talc-based body powder. Since Volume 93, more consistent positive associations for ever-use versus never-use have been reported in pooled cohort studies and case-control studies, including evidence of an exposure–response relationship with frequency or duration of use.^{9,10} However, bias from differential exposure misclassification could not be excluded based on a bias analysis conducted by the Working Group and confounding by asbestos contamination of the talc also could not be ruled out. In two largely overlapping studies in the pulp and paper industry, where potential asbestos coexposure was not adequately considered, an excess risk of ovarian cancer was observed among women exposed to talc. Studies of workers in mines where asbestos absence has been documented were given higher weight. In these studies, which did not include women, no excess risk of lung or stomach cancer was observed. The evidence for these cancers was therefore considered “inadequate”.

In SD rats exposed by inhalation, talc caused bronchioloalveolar carcinoma, bronchioloalveolar adenoma or carcinoma (combined), malignant pheochromocytoma, benign or malignant pheochromocytoma (combined), bilateral benign pheochromocytoma, and bilateral malignant pheochromocytoma of the adrenal medulla in females;

and benign, malignant, or complex pheochromocytoma (combined) of the adrenal medulla in males.¹¹ A significant positive trend in males and females for the incidence of pheochromocytomas (benign, and the combination of benign, complex, or malignant tumours in males; malignant, and the combination of benign or malignant tumours in females) was also observed. The rationale for “sufficient” evidence included the unusual tumour types reported by this study (ie, bilateral malignant pheochromocytomas); and that tumours were observed in both sexes in a study conducted under Good Laboratory Practice.¹¹

Talc induces chronic inflammation; in experimental systems in vivo, consistent and coherent evidence was observed in various tissues following different routes and exposures of up to 2 years.¹¹ Talc alters cell proliferation, cell death, or nutrient supply; talc promoted anchorage-independent growth in human primary and immortalised ovarian epithelial cells. Talc-exposed human primary mesothelial cells secreted factors that promoted fibroblast proliferation. Additionally, multiple studies showed hyperplasia in the respiratory system of rodents exposed chronically by inhalation or acutely by intratracheal administration.¹¹ The consistent and coherent mechanistic evidence was based on studies in which asbestos contamination of talc was highly unlikely.

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- 1 International Agency for Research on Cancer. Volume 136: Talc and acrylonitrile. Lyon, France; June 11–18, 2024. IARC Monogr Identif Carcinog Hazards Hum (in press).
- 2 Koutros S, Lubin JH, Graubard BI, et al. Extended mortality follow-up of a cohort of 25,460 workers exposed to acrylonitrile. *Am J Epidemiol* 2019; **188**: 1484–92.
- 3 Scélo G, Constantinescu V, Csiki I, et al. Occupational exposure to vinyl chloride, acrylonitrile and styrene and lung cancer risk (Europe). *Cancer Causes Control* 2004; **15**: 445–52.
- 4 National Toxicology Program. Toxicology and carcinogenesis studies of acrylonitrile (CAS No. 107-13-1) in B6C3F1 mice (gavage studies). *Natl Toxicol Program Tech Rep Ser* 2001; **506**: 1–201.
- 5 Johannsen FR, Levinas GJ. Comparative chronic toxicity and carcinogenicity of acrylonitrile by drinking water and oral intubation to Spartan Sprague-Dawley rats. *Toxicol Lett* 2002; **132**: 197–219.
- 6 Maltoni C, Ciliberti A, Cotti G, Perino G. Long-term carcinogenicity bioassays on acrylonitrile administered by inhalation and by ingestion to Sprague-Dawley rats. *Ann NY Acad Sci* 1988; **534**: 179–202.
- 7 Walker VE, Fennell TR, Walker DM, et al. Analysis of DNA adducts and mutagenic potency and specificity in rats exposed to acrylonitrile. *Chem Res Toxicol* 2020; **33**: 1609–22.
- 8 Walker VE, Walker DM, Ghanayem BI, Douglas GR. Analysis of biomarkers of DNA damage and mutagenicity in mice exposed to acrylonitrile. *Chem Res Toxicol* 2020; **33**: 1623–32.
- 9 O'Brien KM, Tworoger SS, Harris HR, et al. Association of powder use in the genital area with risk of ovarian cancer. *JAMA* 2020; **323**: 49–59.
- 10 Terry KL, Karageorgi S, Shvetsov YB, et al. Genital powder use and risk of ovarian cancer: a pooled analysis of 8,525 cases and 9,859 controls. *Cancer Prev Res (Phila)* 2013; **6**: 811–21.
- 11 National Toxicology Program. Toxicology and carcinogenesis studies of talc (CAS No. 14807-96-6) (non-asbestiform) in F344/N rats and B6C3F1 mice (inhalation studies). *Natl Toxicol Program Tech Rep Ser* 1993; **421**: 1–287.